REMARKS

Claims 1-5 are herewith amended through the introduction of the subject-matter of claim 16, thereby specifying that the oligonucleotides employed are complementary to, but out of phase with, the nucleotide sequences to be detected.

The Applicant respectfully disagrees with the Examiner's assessment of the cited documents, and herewith provides the following remarks in response to the previously presented claim rejections under 35 USC § 102 and 35 USC § 103.

Remarks in response to claim rejections under 35 USC § 102

The claims as amended essentially describe a method for determining the presence of a genetic element in a nucleic acid sample comprising the steps of providing the nucleic acid sample comprising the genetic element, providing oligonucleotide(s) that are completely or partially complementary to, but that are out of phase with, the region(s) comprising the genetic element(s) of said nucleic acid sample, annealing said oligonucleotide(s) to said nucleic acid sample, ligating said oligonucleotide(s) annealed to said nucleic acid sample to each other using a ligase enzyme, and detecting pyrophosphate to determine whether a ligation reaction has occurred, as a measure of the presence of the genetic element(s).

The Applicant respectfully asserts that previous claim 16, which, by way of this amendment, has been incorporated into claims 1-5 is not anticipated by the prior art, and specifically not by Jansson *et al.* (US 2008/0044813A1), since Jansson *et al.* is completely silent with regard to the feature of using oligonucleotides that are out of phase with the genetic element to be detected.

Analogously, Schultz *et al.* and Schalling *et al.* are also completely silent with regard to the feature of using out of phase oligonucleotides, meaning that these documents do not anticipate the present invention as currently claimed.

Thus, the present invention as claimed is not anticipated by the prior art, and the Applicant consequently respectfully requests that the rejections under 35 USC § 102 are cancelled.

Remarks in response to claim rejections under 35 USC § 103

Claims 1-6, 8-12, 14-15 17-25 are all non-obvious in view of the cited disclosures, as the person having ordinary skill in the art would not know how to solve the problem of devising a step-wise method for rapid, accurate, quantitative analysis of genetic variation without knowing the amount of sample nucleic acid, since neither cited document is concerned with the use of oligonucleotides that are out of phase with the genetic element to be detected.

Jansson *et al.* is considered to constitute the closest prior disclosure, as it teaches a method for detecting ligase-catalyzed joining of nucleic acid ends, where the detection is based on the release of AMP. The difference between Jansson *et al.* and the present invention as currently claimed is i.a. the fact that the present invention employs oligonucleotides that are

out of phase with the genetic element to be detected. Utilizing out of phase oligonucleotides, unlike in-phase oligonucleotides, implies that it is possible to detect a genetic element without knowing the amount of template nucleic acid, since there is no risk for multiple hybridizations and ligations when using out of phase oligonucleotides.

Thus, the present invention as currently claimed solves an important problem within the art, viz. how to provide rapid, accurate, and quantitative analysis of genetic variation, with optimal detection conditions, without knowing the amount of sample nucleic acid.

Schultz *et al*. is merely concerned with determining the presence or absence of a predetermined (known) nucleic acid target sequence through depolymerising the 3' end of an oligonucleotide probe hybridized to a target sequence, to release one or more identifier nucleotides. Consequently, Schultz *et al*. bears no resemblance whatsoever to the instant invention, since the present claims specify that the employed oligonucleotides are out of phase with respect to the region comprising the genetic element. The methodology disclosed in Schultz *et al*. merely pertains to the detection of the presence or absence of a known target sequence through the hybridization of a nucleic acid probe (said probe being unambiguously designed to anneal to a specific sequence, thereby being in phase *per se*), and Schultz *et al*. is further completely unaware of and unconcerned with ligating out of phase oligonucleotides to a genetic element in order to enable accurate detection of for instance repeat sequences.

Schalling *et al*. relies on an entirely different detection principle than the present invention, as Schalling *et al*. merely teaches ligation of hybridized repeat oligonucleotides and subsequent detection of the ligation products by electrophoresis, and said disclosure is utterly silent with regard to using out of phase oligonucleotides. Further, the Examiner emphasizes in the outstanding office action that the ordinary practitioner would have a reasonable expectation of success when combining the teachings of Schalling *et al*. and Jansson *et al*., since Schalling *et al*. explicitly teaches the use of repeat sequences. However, since the current claims of the instant invention specifically pertain to the use of out of phase oligonucleotides, in contrast to Schalling *et al*., which merely teaches using repeat oligonucleotides (i.e. oligonucleotides that are in phase), the ordinary practitioner can no longer have a reasonable expectation of success, since the approach in the present invention as claimed is completely different from the teachings of Schalling *et al*.

Further, the teachings of both Schalling *et al*. and Schultz *et al*. are entirely incompatible with the teachings of Jansson *et al*. (e.g. since they are all based on divergent methodologies with only a limited number of features in common), meaning that the skilled artisan would not find any incentive to combine said disclosures to arrive at the invention.

In summary, since neither cited document mention the use of out of phase oligonucleotides, the skilled artisan would not even be aware of the possibility of utilizing this advantageous approach for determining the presence of a genetic element, meaning that the present invention as claimed is not obvious in view of the cited documents.

Thus, the present invention as currently claimed is not obvious in view of the prior art, and the Applicant consequently respectfully requests that the 35 USC § 103 rejections are cancelled.

Concluding remarks

In the event there are any questions concerning this response, or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of the application may be expedited. In case the Examiner is contemplating issuing a final rejection, the Applicant respectfully requests the Examiner to telephone the undersigned to discuss the matter, in order to expedite prosecution.

No additional fees are believed to be due at this time beyond the fee for three months time extension and RCE. However, if necessary to effect a timely response the Commissioner is authorised to deduct the necessary fees from Deposit account No. 501249.

Respectfully submitted,

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